WAIVER REQUEST

Chlormequat chloride: Request for Waiver from the Conduct of:

OCSPP 870.7800 Immunotoxicity

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I. INTRODUCTION

Taminco (Eastman) is submitting an application for Section 3 registration for chlormequat chloride (CCC). Chlormequat chloride ((2-chloroethyl) trimethylammonium chloride) belongs to the quaternary ammonium class of chemicals. Currently, CCC is registered in the US as a plant growth regulator (PGR) for nonfood uses by other registrants. An immunotoxicity study in accordance with OCSPP Guideline 870.7800 is listed as a data requirement for registration of food use pesticides and would be a requirement for CCC registration. However, the USEPA has issued a memorandum entitled "A Retrospective Analysis of the Immunotoxicity Study." In that document, the Agency presented the results from the immunotoxic evaluations of 155 chemicals. This retrospective analysis showed that 15 of the 155 chemicals yielded positive results in the immunotoxicity assay. The document also included guidance for requesting a waiver from the conduct of the immunotoxicity requirement. The purpose of this document is to provide information relevant to granting a waiver from the conduct of the immunotoxicity study for CCC.

II. SUMMARY OF RELEVANT TOXICOLOGY STUDIES

A number of repeated dose oral toxicity studies with CCC in rats were evaluated by Taminco and were included in a European DAR that are relevant to evaluation of the potential immunotoxicity of CCC. The key endpoints for immunotoxicity evaluation were hematology (effects on white blood cells), spleen weight and histopathological changes, thymus weight and histopathological changes and lymph node histopathological changes. Review of the study reports show that the following immunotoxicity parameters were evaluated in the studies listed below.

Study Type (MRID no.)	Hematology*	Spleen Weight	Thymus Weight	Spleen Histopath.	Thymus Histopath.	Lymph Node Histopath.
90-day oral- rat (163408)	X	X	-	X	X	X
Chronic toxicity- rat (46715205)	X	X	-	X	X	X
Oncogenicity- rat (46715203)	X	X		X		X
Oncogenicity- Mouse (46715204)	X**	X	-	X	X	X
Chronic toxicity- Dog (46715201)	X	X	-	X	X	X

* red blood cell parameters, total leukocyte count and differential leukocyte counts
** differential leukocyte counts only.

Based on the studies conducted with CCC, the main effect seen was decreased body weights and body weight gains at high doses. The results from the relevant CCC studies are summarized as follows:

STUDY TYPE	TOXICOLOGIC FINDINGS
90-day oral- rat MRID 00163408	Dietary concentrations of 0, 300, 900 or 2700 ppm (equivalent to 0, 20.6, 61.3, and 188.5 mg/kg/day in males and 0, 24.4, 72.9, and 220.1 mg/kg/day in females). No adverse treatment-related effects were noted in mortality, clinical signs, food consumption, food efficiency, hematology, clinical chemistry, urinalysis, organ weights, or gross or microscopic pathology. At 2700 ppm, both body weight and overall body weight gain were decreased for in males. No treatment-related effects on body weight were observed in females. The LOAEL was 2700 ppm based on decreased body weight and body weight gain in males. The NOAEL is 900 ppm (approximately equivalent to 61.3 mg/kg/day in males and 72.9 mg/kg/day in females).
Chronic toxicity/ oncogenicity- rat MRID 46715202 MRID 46715203 MRID 46715205	Dietary concentrations of 281, 937 and 2,811 ppm. There were no test substance related mortalities, or signs of clinical toxicity in any of the treatment groups. There were no test substance related effect on body weight and food consumption in the 281 ppm and 937 ppm groups. There were no test substance related changes in the haematological and clinical chemical examinations as well as in urinalysis and ophthalmoscopy. Cholinesterase activities were unaffected. There were no treatment related effects on organ weights. Gross- and histopathological examinations did not show test substance related effects at any dose levels. There was no test substance related increase in the incidence of any neoplasia in any group. At the 2811 ppm concentration, body weight gain was reduced in and females with subsequently reduced terminal body weights. Food consumption was reduced in the males at this concentration from week 54 onwards. Based on the results from this study , the NOAEL in this study was 937 ppm, (43 mg/kg bw) based on the reduced bodyweight gain seen at 2811 ppm. .
Oncogenicity- Mouse MRID 46715204	Dietary concentrations of 150, 600 and 2,400 ppm. There were no test substance related mortalities or signs of clinical toxicity in any of the treatment groups. The body weight of the males the 600 and 2,400 ppm groups were reduced in both groups (<10%, P<0.01). A similar depression was seen in females at the same dose levels (although not statistically significant). These depressions are of questionable biological relevance given their small magnitude and lack of dose response. Body weights in all groups were also comparable to the controls, at the end of the 110 week treatment period. There were no effects on food consumption. Differential white blood cell counts showed no treatment related effect. Treatment had no discernible effect on organs weights, absolute or relative at interim or terminal sacrifice. Gross and histopathological examinations did not show test substance related effects at any dose level.

STUDY TYPE	TOXICOLOGIC FINDINGS
Chronic toxicity-Dog MRID 46715201	Dietary concentrations of 0, 150, 300 and 1,000 ppm. (equivalent to 5, 10, 32 mg/kg bw/day, both sexes). No treatment-related adverse effects observed on food consumption, food efficiency, ophthalmoscopic examination, brain cholinesterase, hematology, clinical chemistry, urinalysis,organ weights, gross pathology, or histopathology. Toxicity was generally related to decreased body weight and body weight gain and clinical signs of toxicity in the 300 ppm and 1000 ppm groups and neurotoxicity in the 1000 ppm dogs. At 1000 ppm, one male dog died on Day 42 and one female dog died on Day 20. All other animals survived until scheduled sacrifice. Clinical signs of neurotoxicity were observed in the animals that died, including: emaciation, apathy, staggering gait, lateral position, saltatory spasm, and vomitus in the male and unsteady gait in the female. The LOAELwas 300 ppm based upon salivation (both sexes), vomiting (in females), and diarrhea (in males), and decreases in body weight gains in males. The NOAEL was 150 ppm (approximately equivalent to 5 mg/kg/day).

III. STRUCTURAL SIMILARITY TO OTHER CHEMICALS

In 1988, USEPA issued PR Notice 88-2 outlining "Clustering of Quaternary Ammonium Compounds". It was determined that the quaternary ammonium compounds can be grouped into 4 broad categories based on these diverse chemical structures. Group I quaternary ammonium compounds included alkyl or hydroxy alkyl, straight chain substituted compounds with didecyl dimethyl ammonium chloride (DDAC) as the representative chemical for this group. Although not specifically listed, CCC is structurally similar to these quats. Two quaternary ammonium compounds were among the 155 chemicals listed in the Agency's retrospective analysis. These quaternary ammonium compounds were not considered immunotoxic.

IV. RATIONALE FOR WAIVER

Subchronic and chronic dietary toxicity studies in rats, mice and dogs were were conducted with chlormequat chloride in which parameter relevant to immunotoxicity were evaluated. The primary effect seen with CCC exposure was decreased body weights and body weight gains. No evidence of immunotoxicity was seen upon evaluation of white blood cell counts and differential, spleen weights or histopathology of the spleen, thymus or lymph nodes in any of the studies. Structurally, CCC is a quaternary ammonium compound similar to didecyl dimethyl ammonium chloride (DDAC). Two quaternary ammonium compounds were among the 155 chemicals listed in the Agency's retrospective analysis. These quaternary ammonium compounds were not considered immunotoxic.

V. CONCLUSION

Based on the above considerations, Taminco hereby requests a waiver for chlormequat chloride from the conduct of OCSPP 870.7800 Immunotoxicity

VI. REFERENCES

MRID 46715201 Mellert, W. (1993) Report on the Study of the Toxicity of Chlormequat-Chloride in Beagle Dogs Administration via the Diet over 12 Months. Project Number: 33D0580/87120, 1993/11109. Unpublished study prepared by BASF Aktiengesellschaft, Dept. of Toxicology. 879 p.

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MRID 46715203 Mellert, W. (1992) Study of the Potential Carcinogenic Effect of Chlormequat-Chloride in Wistar Rats Administration via the Diet over 24 Months. Project Number: 71S0580/87047, 1992/11094. Unpublished study prepared by BASF Aktiengesellschaft, Dept. of Toxicology. 1651 p.

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USEPA (2006).Reregistration Eligibility Decision for Aliphatic Alkyl Quaternaries (DDAC).EPA739-R-06-008. August 2006.

USEPA (2013).A Retrospective Analysis of the Immunotoxicity Study (OCSPP Test Guideline No. 870. 7800)